REMARKS

Reconsideration of the above-identified application in view of the amendment above the remarks below is respectfully requested.

No claims have been canceled or added in this paper. Claims 1, 6 and 43 have been amended in this paper. Therefore, claims 1-31 and 35-44 are pending. Of these claims, claims 35-42 have been withdrawn as being directed at non-elected Groups. Therefore, claims 1-31 and 43-44 are under active consideration.

Claims 1-31, 43 and 44 stand rejected under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In support of the rejection, the Patent Office states the following:

> Claims 1 and 43 each recite the limitation "concluding from the said knowledge base on the biological effect and/or activity of said at least one drug and/or pharmaceutical composition of said biological sample A from step (a)" (see for example, lines 16-18 of claim 1 and lines 19-21 of claim 43). This limitation causes the metes and bounds of the claim to be indefinite because the recited limitation is ambiguous as to what is actually concluded from "the said knowledge base on the biological effect and/or activity of said at least one drug and/or pharmaceutical composition of said biological sample A from step (a)." Claims 2-31 and 44 are also included under this rejection due to their dependence from either claim 1 or 43.
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> For purposes of continuing examination, the limitation "concluding from the said knowledge base on the biological effect and/or activity of said at least one drug and/or pharmaceutical composition of said biological sample A from step (a)" has been construed to read on concluding from said knowledge base a biological effect and/or activity that said at least one drug and/or pharmaceutical composition has [on] said biological sample A in step (a) of the claimed process.

Applicants have amended claims 1 and 43 in the manner suggested by the Patent Office. Accordingly, the subject rejection has been overcome and should be withdrawn.

Claims 1-31, 43 and 44 stand rejected under 35 U.S.C. 101 "because the claimed invention is directed to non-statutory subject matter." In support of the rejection, the Patent Office states the following:

> Claims 1-31, 43, and 44 are drawn to a process for determining the biological effect and/or activity of at least one drug and/or pharmaceutical composition. The claimed process comprises the abstract steps of analyzing cytosine methylation at chosen DNA site, selecting differentially methylated sites in said chosen DNA sites to generate a knowledge base, and concluding from said knowledge base the biological effect and/or activity of said at least one drug and/or pharmaceutical composition and, therefore, involves the application of a judicial exception. Regarding inventions involving the application of a judicial exception, said application must be a practical application of the judicial exception that includes either a step of a physical transformation, or produces a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)). In the instant claims, there is no step of physical transformation that results from said application of judicial exception, thus the Examiner must determine if said application of a judicial exception produces a useful, concrete, and tangible result.
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> In determining if the application of a judicial exception produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a result to be "useful," the application of a judicial exception must produce a result that is specific, and substantial. For a result to be "concrete," the application of a judicial exception must have a result that is reproducible. For a result to be "tangible," the application of a judicial exception must produce a real world result. Furthermore, the claim must be limited only to statutory embodiments.

> Claims 1-31, 43, and 44 do not produce a tangible result. A tangible result requires that the claim must set forth a practical application of a judicial exception to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that a result of the application of a judicial exception is outputted to a display, a user, a readily accessible memory or other computer on a network, or by including a physical transformation.

Without acquiescing in the propriety of the rejection, Applicants have amended claims 1 and 43 to adopt the language suggested by the Patent Office. Accordingly, the subject rejection has been rendered moot and should be withdrawn.

Claims 1-11, 13-21, 23-26, 28, 31, 43 and 44 stand rejected under 35 U.S.C. 102(e)(2) "as being anticipated by Laird et al. (P/N 6,311,393 B1) in light of Klippel et al. (P/N 3,558,768)." In support of the rejection, the Patent Office restates the reasons from its January 12, 2005 Office Action and then states the following:

> The instant claims are drawn to methods for determining the biological effect and/or activity of at least one drug, chemical substance, and/or pharmaceutical composition comprising the steps of obtaining a biological sample A containing DNA, wherein said sample A was exposed to said at least one drug, chemical substance, and/or pharmaceutical composition, obtaining a biological sample B containing DNA, wherein said sample B was not exposed to said at least one drug, chemical substance, and/or pharmaceutical composition, subsequently analyzing the level of cytosine methylation at chosen sites of the DNA contained in samples A and B, selecting sites which are differentially methylated between the DNA in said samples to generate a knowledge base, and concluding the biological effect of said at least one drug, chemical substance, and/or pharmaceutical composition from said knowledge base.
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> Laird et al. disclose a method for determining methylation patterns (biological effect or activity) in genomic DNA (containing genes) after being treated with sodium bisulfite (sample A)(at least one drug and/or pharmaceutical composition)(see Laird et al.,

abstract), as stated in instant claims 1, 9, and 13. Klippel et al. is further relied upon in the instant rejection to demonstrate the use of sodium bisulfite in pharmaceutical compositions (see Klippel et al. col. 3, line 30 through col. 4, line 36). Laird et al. disclose methylation amounts in multiple samples are quantitatively determined based on reference to a control reaction (sample B)(see Laird et al., col. 5, lines 61-64) which represents an unexposed sample and analyzing methylation levels in samples A and B, as stated in instant claims 1 and 43. Laird et al. disclose using probes and primers to distinguish between methylated and unmethylated nucleic acid, amplifying the DNA, and detecting methylated DNA via fluorescence-based quantitative PCR (see Laird et al., col. 5, lines 16-64) which represents selecting sites differentially methylated. Figures 7 and 8 display data that represent a knowledge base generated based on the conclusive effect of sodium bisulfite treatment, as recited in instant claims 1 and 43. The gene names (i.e. ESR1 or MyoD1) in Figures 7 and 8 represent additional information used for the conclusion data found in these figures (i.e. correlation between MLH1 gene expression, MSI status, and promoter methylation status of MLH1 in Figure 8, col. 24, lines 30-31), as stated in instant claim 24. The x-axes in the 2-graphs of represent at least two individual rows of analyses, as stated in instant claims 17 and 25. This data presentation also shows all or a part of the sites used for the conclusion, as stated in instant claim 23. Further conclusions are drawn by Laird et al. (see Laird et al., col. 24, lines 48-67). Laird et al. disclose in higher order eukaryotic organisms, DNA is methylated only at cytosines located 5' to guanosine in the CpG dinucleotide (see Laird et al., col. 1, lines 14-17) which represents cytosine methylation. Laird et al. disclose contacting a DNA sample from a patient with a modifying agent, bisulfite (see Laird et al., col. 5, lines 19-20 and 31), as recited in claim 44. Laird et al. disclose various methods to identify altered methylation sites in cancer cells (see Laird et al, col. 3, lines 3-5) and determining DNA methylation patterns at specific loci (see Laird et al, col. 4, lines 12-15) which represents only one set of selected sites, as stated in instant claim 18. Laird et al. disclose selecting genes (see Laird et al., col. 19, line 5) which represents a knowledge base of different classes, as stated in instant claim 19. Laird et al. disclose using PCR, sequencing, fluorescent labeling (see Laird et al., col. 7, lines 26-65), as stated in instant claim 9. Laird et al. disclose using human colorectal adenocarcinoma (cancer) and normal nucosa (healthy) tissue samples (see Laird et al., Figures 7 and 8; col. 22,

lines 46-49), as stated in instant claims 4 and 5. Laird et al. disclose 25 match-paired normal and tumor samples with MLH1 expression level and MLH promoter methylation as well as MYOD1 control gene (see Laird et al., Figure 8 and col. 8, line 64 to col. 9, line 12) which represent at least two methylation sites selected and analyzed in parallel, as stated in instant claims 11 and 21. Laird et al. disclose using parallel reactions with methylated, unmethylated, and control oligos of bisulfite-treated DNA samples (see Laird et al., col. 18, lines 36-39). Laird et al. disclose analyzing methylation status of the ESR1 locus in DNA samples which is a gene that contains hypermethylatable CpG islands that undergo de novo methylation in human colorectal tissue in all normal and tumor samples (see Laird et al., col. 18, line 67 to col. 19, line 17 and col. 22, lines 29-30) which represents methylation sites that are located in methylation relevant genes associated with cancer, as stated in instant claim 14. Laird et al. disclose using PCR primers and probes used for sequences representing fully methylated and fully unmethylated DNA in several genes, including ESR1 (col. 19, lines 32-40), which represents analyzing all potential methylation sties of the DNA, as stated in instant claim 10. Laird et al. disclose isolating DNA via proteinase K digestion from sperm and HCT116 (human colorectal cell line), treated with sodium bisulfite, and then the DNA samples are analyzed by COBRA analysis or amplification process using fluorescence-based real-time quantitative PCR (see Laird et al., col. 16, line 55 to col. 17, line 17), as stated in instant claims 6-8. Laird et al. disclose that altered DNA methylation pattern of cytosine residues is mutagenic (see Laird et al., col. 2, lines 34-36) demonstrates that the colorectal samples mentioned above represent genes related with ulcerative colitis which is a type of colon disease, as stated in instant claim 15. In Example 4, Laird et al. disclose analyzing the methylation DNA samples from the same patient (col. 22, lines 29-32) which represents analyzing methylation sites that are personalized, as stated in instant claims 16 and 28. In Example 5, Laird et al. disclose using 25 patients with tumor and normal tissue samples surgically removed (dissected tissue immediately frozen)(see Laird et al., col. 23, lines 28-37) which represents histologically, dissected biological material from healthy and diseased individuals in instant claims 2-4. Laird et al. disclose the use of paraffin embedded samples (see Laird et al., col. 9, lines 42-46). Laird et al. disclose using the TaqMan, Lightcycler, Sunrise technologies, as well as ABI Prism 7700 Sequence Detection System (see Laird et al., col. 14, lines

> 5-20) which represent selection at least partially performed automatically by an automate or computer device and conclusions performed by a computer system, as recited in instant claims 20, 26, and 31.

Later in the Office Action, the Patent Office states the following:

> In regards to the rejection of claims as being anticipated by Laird et al., applicants argue that the instant claims have been amended to recite "at least one drug and/or pharmaceutical composition" and as such, the claims no longer read on sodium bisulfite. Applicants further argue that sodium bisulfite is neither a drug nor a pharmaceutical composition as evident from the fact that sodium bisulfite has no known therapeutic use.
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> In response, it is first noted that neither the instant claims nor the instant specification provides a definition for the terms "drug" or "pharmaceutical composition" that limit said claims to only encompassing chemical substances that have a known therapeutic use. Further, the instant rejection relies upon Klippel et al. to demonstrate the use of sodium bisulfite as an ingredient in pharmaceutical compositions (see Klippel et al. col. 3, line 30 through col. 4, line 36).

Applicants respectfully traverse the subject rejection. Claim 1, from which claims 2-11, 13-21, 23-26, 28 and 31 depend, has been amended herein and now recites "[a] method for determining the biological effect and/or activity of at least one pharmaceutical composition, comprising the steps of:

(a) obtaining a biological sample A containing DNA, said biological sample A being from at least one of an individual, a tissue, a cell or another biological material containing DNA, wherein said biological sample A was exposed to said at least one pharmaceutical composition;

(b) obtaining a biological sample B containing DNA, said biological sample B being from at

least one of an individual, a tissue, a cell or another biological material containing DNA, wherein said biological sample B was not exposed to said at least one pharmaceutical composition;

(c) then, analyzing the level of cytosine methylation at chosen sites of the DNA contained in the biological samples A and B;

(d) selecting those of said chosen sites which are differentially methylated between the DNA in biological samples A and B, whereby a knowledge base is generated; and

(e) concluding from said knowledge base a biological effect and/or activity that said at least one pharmaceutical composition has on said biological sample A in step (a) and outputting the conclusion to at least one of a display, a user, a readily accessible memory and a computer on a network."

Claim 1 is neither anticipated by nor rendered obvious over Laird et al. in light of Klippel et al. This is at least for the reason that Applicants, without agreeing that sodium bisulfite is a drug, have deleted the term "drug" from claim 1. As such, claim 1 is now directed at a method for determining the biological effect and/or activity of at least one "**pharmaceutical composition**," said method comprising, amongst other things, obtaining a biological sample A containing DNA, wherein said biological sample A was exposed to said at least one pharmaceutical composition; obtaining a biological sample B containing DNA, wherein said biological sample B was not exposed to said at least one pharmaceutical composition; and then, analyzing the level of cytosine methylation at chosen sites of the DNA contained in the biological samples A and B. Applicants respectfully submit that sodium bisulfite does not constitute a "pharmaceutical composition." This is because,

amongst other things, the term "pharmaceutical composition" is understood by those of ordinary skill in the art to mean a composite of multiple components. Since sodium bisulfite is merely one component, sodium bisulfite, by itself, cannot constitute a "pharmaceutical composition."

Claim 43, from which claim 44 depends, is patentable for the same reasons given above for claim 1. In addition, claim 43 is also patentable because claim 43 requires, amongst other things, that the following two steps be performed sequentially: (1) that biological sample A be obtained, wherein biological sample A **was** exposed to said at least one pharmaceutical composition; and (2) **thereafter**, that the level of cytosine methylation at chosen sites of the DNA contained in biological sample A be analyzed, wherein said analyzing comprises chemical treatment of biological sample A with at least one of bisulfite, hydrogen sulfite or disulfite. The Patent Office is apparently contending that the sodium bisulfite of Laird et al. represents "at least one of a drug or a pharmaceutical composition." However, whereas the claim requires that the chemical treatment with at least one of bisulfite, hydrogen sulfite or disulfite occur **after** biological sample A **was** already exposed to the pharmaceutical composition, the bisulfite treatment of Laird et al. is only performed once. **Consequently, the single bisulfite treatment of Laird et al. cannot simultaneously satisfy both step (a) of claim 43 and step (c) of claim 43.**

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Applicants note that claims 12, 22, 27, 29, 30 have not been rejected on the basis of any prior art. Therefore, in view of the fact that the only bases under which these claims have been rejected have been overcome in this paper, Applicants respectfully request that claims 12, 22, 27, 29 and 30

be allowed at once.

In conclusion, it is respectfully submitted that the present application is now in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on August 3, 2007

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